IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	:	09/972,916	Confirmation No.: 4645
Applicant	:	Peter M. THULÉ, M.D.	
Filed	:	October 10, 2001	
Title	:	GLUCOSE SENSITIVE REGULATOR OF INSULIN TRANSCRIPTION	
Group Art Unit	:	1635	
Examiner	:	ANGELL, Jon E.	
Atty. Docket No.	:	US 1292/01(VA)	

DECLARATION OF PETER M. THULÉ
UNDER 37 CFR § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Peter M. Thulé, M.D., hereby declare and state as follows:

1. I am the sole inventor of the above-captioned application S.N. 09/972,916 (hereinafter "the '916 application") filed October 10, 2001, which claims priority on prior U.S. Provisional Application S.N. 60/239,113, filed October 11, 2000.

2. I graduated from the University of California (Berkeley) in 1979, and from Justus-Liebig University (Giessen, Germany) in 1986, obtaining B.A. and M.D. degrees, respectively. I completed my Postgraduate training in Internal Medicine, at the Emory University, Atlanta, Georgia (1987-1990) and Clinical and Research Fellowship in Diabetes, Endocrinology and Metabolism, at the Emory University (1991-1995).

3. I am a member of various clinical, safety, and research and development committees, and a member of the Diabetic Advisory Council, at the U.S. Department of Veterans Affairs Medical Center (Atlanta, Georgia).

4. I am a manuscript *ad hoc* reviewer for several medical journals.

5. I have received numerous grants from the National Institutes of Health (NIH), the VA, and various educational institutions.

6. I am the principal author of multiple, peer-reviewed publications, abstracts and letters.

7. I am currently an Associate Professor of Internal Medicine at the Emory University School of Medicine (Atlanta, Georgia). I am also the fellowship training program Director of the Division of Endocrinology, Metabolism & Lipids.

8. I am currently also a Faculty Member at the Petit Institute for Bioengineering and Bioscience (Georgia Institute of Technology).

9. I am currently also the Acting Chief of the Section Endocrinology & Metabolism at the Atlanta VA Medical Center.

10. A copy of my full Curriculum Vitae (16 pp.) is attached.

11. I have reviewed and am familiar with the Office Action of April 2, 2009 (and various previous Office Actions), issued by the U.S. Patent and Trademark Office in the '916 application.

12. In the Office Action of April 2, 2009, Examiner Angell introduced a new ground of rejection for Claims 1-15, under 35 U.S.C. §103(a) as being unpatentable over various Thulé et al. abstracts (Diabetes May 1999, supplement, Abstract from meeting of June 9-13, 1999, and Abstract from meeting of June 1998 - all previously cited) in view of Thulé and Liu presentation at the ADA 59th Annual Meeting, June 1999 (provided as Reference 3 in the IDS filed 3/14/2006) and further in view of Goswami et al. (Endocrinology 1994, Vol. 134, pages 736-743), Vaulont et al. (J. Mol. Biol. 1989, Vol. 209, pages 205-219) and Cognet et al. (J. Mol. Biol. 1987, cited by Applicants).

13. Examiner Angell admitted that none of the three Thulé abstracts provide the actual nucleotide sequence of the promoter element(s) of the claimed vector; however, he concluded that one of ordinary skill in the art would have been motivated to make the vector based on the teachings of the Thulé abstracts, and that the Thulé abstracts provide evidence of expectation of success.

14. Examiner Angell also cited various Thulé and Liu presentations, and Goswami et al., Vaulont et al., and Cognet et al. publications, and concluded that it would have been obvious to one of ordinary skill in the art, at the time of the filing, to make the vector of Thulé abstracts in view of the Thulé and Liu presentations, and further in view of Cognet et al., Vaulont et al., and Goswami et al. publications, with a reasonable expectation of success.

15. At the time the present invention was made, several other investigators in the art pertaining to the invention, had attempted to utilize a native L-PK promoter, alone or with enhancer elements, for expression in non-native environment, but failed.

A. In particular, Bergot et al. (Nuc. Acids Research, 20(8):1871-1878, 1992), note that "The effect of the L4-L3 [the L-PK GIRE] cooperation in promoting cyclic AMP-dependent transcription inhibition and strong glucose dependant stimulation seems therefore to be lost in the context of the TK [thymidine kinase, heterologous] promoter." See the Results section, page 1876, left column, ¶1. They further note at page 1876, left column, line 9 from bottom, "that L4L3 cooperation seems to be active only in the context of the L-PK promoter, and not when both elements are ligated upstream of the TK promoter,.... According to this hypothesis, any displacement of the L-PK elements away from the TATA box, or intercalation of supplementary binding sites for different proteins between the L-PK elements and TATA box is expected

to disturb the hypothesized normal interactions and hence the response to modulators." See Bergot et al., page 1876, left column, line 2 from bottom, to right column, line 4. These statements indicate that the glucose responsive L-PK promoter region might not be functional in a non-native promoter, such as the IGFBP-1 basal promoter.

Mitanchez et al. (Endocrine Reviews, 18(4):520-540, 1997) and Mitanchez et al. (FEBS Letters 421:285-289, 1998), describe utilizing the L-PK promoter to drive expression of an insulin coding sequence in transgenic mice. They successfully expressed insulin in the livers of these animals. However, despite obtaining mouse lines with up to 130 copies of the transgenic insulin gene in each cell, insulin production was insufficient to correct hyperglycemia when the animals were made diabetic. This information clearly indicates that other investigators had attempted to utilize the L-PK promoter alone to drive transgenic insulin expression for the treatment of diabetes mellitus, and had failed.

Mitanchez et al., above, write about modifying the L-PK promoter using enhancer elements from the aldolase B gene. While this particular approach was not published, one group (Chen R. et al., Mol. Therapy 3(4): 584-590, 2001) did subsequently publish an insulin gene therapy approach utilizing the aldolase B enhancer elements coupled to the glucose-6-phosphatase promoter, another glucose inducible promoter. While this chimeric promoter attenuated

hyperglycemia in diabetic rats, it failed to reduce blood sugars to normal in fed animals.

Lee et al. (Nature 408: 483-488, Nov. 2000) reported the use of the L-PK promoter, coupled to an enhancer element, to normalize blood sugars in diabetic rats and mice using adeno-associated virus (AAV). They demonstrated glucose responsiveness of their insulin transgene in animals. However, the article was later withdrawn by three of the five authors (Nature 458:660, 2009) because they had failed to reproduce the results. One author was deceased, leaving only one maintaining that the results were still valid.

16. The nucleotide numbering presented in the Thulé and Liu presentation slide does not correlate with the claimed sequences. For instance, the numbers for the IGFBP-1 sequences indicate that the $(GIRE)_3$BP-1 promoter portion is limited to bases -111 to 96+ of IGFBP-1. However, the sequence in SEQ ID NO: 5 of the claimed invention, encompasses bases spanning -115[1] to +105 relative to the IGFBP-1 transcription start site. Likewise, the L-PK promoter sequence numbers presented by the Thulé and Liu presentation, -173 to -125, also do not correlate. SEQ ID NO: 5 encompasses three head-to-tail repeats of bases best indicated by base numbers -173 to -123, respective to the transcription start site.

[1] Due to a counting error, it was previously presented as -114.

The field of biotechnology is unpredictable. It is well-known that expression and/or functionality of a gene can be entirely affected by, for example, changing, deleting, or skipping, even one base or nucleotide.

17. Currently, there exists no single, widely-accepted numbering system for DNA sequence bases or base pairs with respect to function or replication. The largest most commonly used DNA sequence data bases number entered sequences from 1 onward, relative only to the submitted sequence. All other numberings of DNA sequences must be coupled with a referenced initiation to be useful. Such a reference was not provided in the slide presentation. Published literature referring to both the rat L-PK and rat IGFBP-1 promoters were not uniform in their use of an internal reference, even within authors. Moreover, base numbers in published sequences of rat L-PK and rat IGFBP-1 promoters were inconsistent both within single publications and across publications. Further, published literature is not concordant with respect to promoter sequences, particularly of the rat L-PK promoter. Additionally, the numbers presented in the slide do not correlate with SEQ ID NO: 5. Consequently, the numbers provided in the presentation do not accurately and reliably disclose the claimed sequence of SEQ ID NO: 5.

18. Cognet et al., cited by Examiner Angell, in the Office Action of April 2, 2009, describe the rat L-PK transcription initiation start site as "microheterogeneous," meaning multiple transcripts originate from each of the base pairs from 14-19 base pairs 5' of the ATG translation initiation codon. Therefore, any of the base pairs numbered 14-19 could have been arbitrarily used to assign the base immediately 5' to its transcription initiation site as +1.

19. Cognet et al., Vaulont et al., and Goswami et al. publications do not disclose precisely just the sequences that together make-up the construct of Claim 9, but the longer sequences that appear to overlap with the numbering of the nucleotides disclosed in the presentations. Due to the lack of a single, widely accepted methodology for DNA sequence numbering and the leading uncertainty, one of ordinary skill in the art would not reliably or reasonably expect success in duplicating the elements of the construct of Claim 9.

20. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States

Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

6/3/09
Date

Peter M. Thulé, M.D.

Curriculum Vitae

1. **Peter Martin Thulé, MD**

2. **Office Address:** Atlanta VA Medical Center
Medical Service (111)
1670 Clairmont Rd.
Decatur, GA 30033

Tel: (404) 321-6111 X2079
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3. **E mail Address:** pthule@emory.edu

4. **Place of Birth:** Berkeley, California

5. **Citizenship:** USA

6. **Current Titles and Affiliations:**

Associate Professor of Medicine
Emory University School of Medicine
Dept. of Internal Medicine,
Division of Endocrinology and Metabolism
2003-present

Program Director, Division of Endocrinology, Metabolism, & Lipids
Fellowship Training Program
2005-present

Faculty Member, Petit Institute for Bioengineering and Bioscience (IBB)
Metabolic and Secretory Organs
Georgia Institute of Technology
2005-present

Chief (acting) Section Endocrinology & Metabolism
Atlanta VA Medical Center
2009-present

Staff Physician, Section Endocrinology & Metabolism
Atlanta VA Medical Center
1995-present

7. **Previous Academic and Professional Appointments:**

Assistant Professor of Medicine, Emory University School of Medicine
1995-2003

Clinical Instructor, Emory University School of Medicine,
Diabetes Clinic, Grady Memorial Hospital, Atlanta, Georgia
1990-1991

8. **Previous Administrative Appointments:**

Ethics Committee, VA Medical Center, Atlanta, GA
1996-1999

9. **Licensure:** Georgia, License number 33727, October 11, 1990

10. **Specialty Boards:**

American Board of Internal Medicine, 1990,
Recertification May 2000, Certification awarded 2000 through 2010

American Board of Internal Medicine Subspecialty Board; Diabetes, Endocrinology and Metabolism, 1996, Recertification Examination May 2000, Certification awarded 2004 through 2014

Federal Licensing Examination (FLEX) 1989

11. **Education:**

1979 B.A, Zoology, University of California, Berkeley

1986, M.D., Justus-Liebig University, Giessen, Germany

12. **Postgraduate Training:**

Internship and Residency in Internal Medicine, Emory University Affiliated Hospitals, Atlanta, Georgia, Juha Kokko, MD, PhD, 1987-1990

Clinical and Research Fellowship in Diabetes, Endocrinology and Metabolism, Emory University Affiliated Hospitals, Atlanta, Georgia, Lawrence Phillips, MD, 1991-1995

13. **Committee Memberships:**

Clinic Guidelines Implementation Steering Committee, VISN 7
Dept. of Veterans Affairs 1996-2003

Surgical Case Review Committee, VA Medical
Center, Atlanta, GA 1997- 2007

Radiation Safety Committee, VA Medical Center, Atlanta, GA
1997- Present

Research & Development Committee, VA Medical Center, Atlanta, GA
1997- 2008

Clinical Reminders Implementation Committee, VA Medical Center, Atlanta, GA
2003-2004

Emory University Department of Medicine Education Committee
2006-2008

Emory University Department of Medicine Faculty Development Committee 2006-present

Sub-committee Chair: Faculty Awards
2006-2008

Diabetic Advisory Council, VA Medical Center Atlanta, GA
2004-present

Georgia Tech/Emory Center for the Engineering of Living Tissues (GTEC)
Executive Committee
2009-present

14. **Manuscript *Ad Hoc* Reviewer:**

VA/JDRF Diabetes Research Centers LOI Review Committee, 1997

American Journal of Medical Sciences, 1995-1998

Trends in Molecular Medicine, 2001-present

Gene Therapy, 2001-present

Human Gene Therapy, 2004-present

Journal of Diabetes and its Complications, 2005-present

Molecular Therapy, 2005-present

Diabetes, 2004-present

Transplantation, 2007-present

15. **Honors and Awards:**

VA Merit Review Committee, Endocrinology A, *ad hoc* 2004-2006

National Research Service Award, Individual Award, 1993-1995

NIH Travel Award, NIDDK Symposium on the Impact of Molecular Genetics on the Treatment of Genetic Diseases, 1992

National Research Service Award, Institutional Grant, 1991-1992

Graduated with Highest Honors, University of California, Berkeley 1979

16. **Society Memberships**:

American Diabetes Association, 1995- Present

American Society of Gene Therapy, 1999-Present

American Federation for Medical Research, 1999-Present

The Endocrine Society, 2006-present

17. **Research Focus**:

Development of insulin gene therapy as a treatment for diabetes mellitus, and investigations into hepatocellular effects of ectopic insulin production. Our animal model utilizes a metabolically regulated, hepatic specific gene promoter to drive expression of an insulin transgene in the livers of diabetic rats. Administration of viral vectors containing these promoters coupled to a human insulin cDNA, normalizes blood sugars in diabetic rodents.

18. **Patents**:

Pending: Glucose Sensitive Regulator of Insulin Transcription

19. **Grant Support**:

Active Support:

P.I. *Hepatic Insulin Gene Therapy in Swine* VA Merit $637,200 2009 - 2013

Co-I.NIH, *Diverese Roles of Reactive Oxygen Species in Vascular Disease,* PO1, P.I. Kathy Griendling, Div. Cardiology, Emory University $1,515,000 07/2009-06/2014

Co-P.I., NIH, *Tissue Engineered Substitute Based on a System of Autologous Cells*, NIDDK RO1 DK076801-01, P..I. Athanassios Sambanis, Ga. Tech, $2,145,225, sub-contract $385,000, 2007-2012

Co-I.NIH, PPAR Gamma Regulates Vascular Endothelial Reactive Oxygen Species Production in Diabetes, NIDDK R01 DK074518 - 01A2 P.I.: C. Michael Hart 09/07 – 08/12 $1,500,000

Co-I, VA Merit, *Novel imaging technologies for early diagnosis of diabetic retinopathy.* PI: Tim Duong, $450,000, 2008-2011

Co-I,NIH/NEI R01EY014211-6 *Layer specific oxygenation and blood flow imaging of normal and diabetic retina*, P.I. Tim Duong $1, 000,000 04/01/09-03/30/13

Previous Support:

Co-P.I. JDRF Innovative Award *Bioartificial Matrix to Promote Vascularization of Islets* JDRF: 5-2008-267, P.I. Andrés Garcia, Ga. Tech, $106,265, 2008-2009

P.I, Georgia Tech/Emory Center for Engineering of Living Tissues (National Science Foundation), *Tissue Engineering to Enhance Gene Therapy for Diabetes Mellitus*, $200,088, 2000-2008

P.I., Dept. of Veteran Affairs, *Alterations in Hepatic Glucose Metabolism with Insulin Gene Transfer*, VA Merit Review, $547,000, 2003-2007

Co-Investigator, NIH, *Vascular Inflammation and Advanced Glycation Endproducts*, RO1, NIDDK PA-00-026, P.I. W. Robert Taylor, Emory University $1,783,400 2003-2008

Co-P.I., EMTECH Biotechnology, Inc., *Transplantation of Insulin-Producing Hepatocytes for the Treatment of Insulin-Dependent Diabetes,* Co-P.I. Athanassios Sambanis, Prof. Chem. Eng, Georgia Institute of Technology, $96,960, 2003-2004

P.I., American Diabetes Association, *Effect of hepatic insulin gene therapy on fuel substrate oxidation, food intake, and body weight*, Innovative Award, $72,488, 2001-2004

P.I., Juvenile Diabetes Research Foundation, *Modular Enhancement of Glucose Regulated Insulin Gene Therapy*, Research Grant, $449,596, 2000-2003

P.I., Department of Veterans Affairs, *A model of insulin gene therapy for IDDM*, Merit Review Award, $203,000, 1996-1999

20. **Formal Teaching**:

a. **Medical Student Teaching**:

Instructor, Small Groups, Pathophysiology, 1995-2008

Instructor, Small Groups, Pharmacology, 1995-2008

Instructor, Clinical Methods, M2, 2003-2005

b. **Graduate Program**:

Weekly Endocrine Fellow Board Preparation Review, 2005-present

Pathophysiology Seminar, Endocrinology, 2004-present

Lecturer, Molecular Endocrinology, 1998-2000

Lecturer, Pathophysiology, Biomedical Engineering, Georgia Tech & Emory, 2004-present

21. **Supervisory Teaching**:

a. **Post-doctoral Fellows**:

Darin Olson, MD, PhD, Research Fellow, Endocrinology, Diabetes & Metabolism, 2000-2003

Marty Porter, PhD, Postdoctoral Fellow, 2000-2002

b. **Residency Program**:

Consultation Attending Physician, Fellowship Training Program, Endocrinology, Diabetes & Metabolism, 1995-present

Ward Attending, Atlanta VA Medical Center, Internal Medicine Residency Training Program, 1995-present

c. **Thesis Committees**

Ed Phelps, Bioengineering Doctoral Candidate, Woodruff School of Mechanical Engineering, Petite Institute for Bioengineering and Bioscience, Georgia Institute of Technology: Engineering bioartificial matrices to promote vascularization and survival of transplanted pancreatic islets.

Heather (Virginia) Bara, Doctoral Candidate, Georgia Tech Emory Department of Biomedical Engineering: Engineering physiological secretion of insulin from non-beta cells for the treatment of diabetes mellitus.

Shing-Yi Cheng, Doctoral Candidate, Georgia Institute of Technology, School of Mechanical Engineering: Thesis investigating development and application of glucose sensitive sol/gel transformations to regulate insulin delivery in diabetes mellitus. Received PhD May 2005

Matt Whalin, MD PhD Doctoral Candidate, Emory University, Graduate School of Arts and Sciences, Thesis: Role of the Receptor for Advanced Glycation Endproducts (RAGE) in AGE-induced Oxidative Stress and MCP-1 induction. Received PhD January 2007

Shiue-Cheng (Tony) Tang, Doctoral Candidate, Georgia Institute of Technology, School of Mechanical Engineering: Thesis Toward the Development of a Pancreatic Tissue Substitute: Genetic Engineering of Non-β Cells for Regulated Insulin Secretion, Received PhD June 2004

Sara Paveglio, Masters of Science, Georgia State University: Thesis investigating effect of intrahepatocellular insulin production on expression of genes critical to liver carbohydrate metabolism, June 2003
University of Vermont, Cell & Molecular Biology, 2003-2008, PhD
Post-doctoral training, Department of Immunology, mentor Lynn Puddington, University of Connecticut, 2008-present

d. **Other**:

Undergraduate Research, Nicholas J Nahm, Duke University, June 2004 applications to medical school 2005

Medical Student Summer Research Program 2001, Dana Rodgers, M3

Summer Undergraduate Research Experience (SURE), Research Mentor, 1998, Ashish Patel, accepted to medical school, 1999

PROMISE (Postbaccalaureate Research Opportunities for Minorities in the Biomedical Sciences) Scholar, Research Mentor, Sean DeSouza, BS. 2005-2006

22. **Invited Speaking Engagements and Grand Rounds:**

The Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech & Emory Department of Surgery Joint Workshop, Emory University, Toward Regulated Insulin Secretion

from a Tissue Engineered Construct, May 2, 2009

Bioengineering and Biosciences Unified Graduate Students (BBUGS) Seminar, Diabetes and Gene Therapy, Georgia Tech/Emory Center for Engineering of Living Tissues, October 29, 2008

New Advances in Hepatic Insulin Gene Therapy, 50th Anniversary Lecture Series, Clinical Research Center, The First Affiliated Medical School Hospital, Xi'an Jiaotong University, Xi'an, Shaanxi, China October 27, 2007

Regenerate 2005, Pittsburgh Tissue Engineering Initiative, Non-Islet Tissues in the Treatment of Diabetes Mellitus, Atlanta, GA, June 3, 2005

Ninth Annual Hilton Head Workshop, Engineered Tissues- 2005, "Long-Term Glycemic Control after Delivery of a Metabolically Responsive Insulin Transgene By Pseudotyped, Self-Complementary AAV (SC-AAV2/8) to STZ-Diabetic Mice"

Conference on Genomics and Society, University of Kerala, Kariavattom, Thiruvananthapuram, India, "Progress in hepatic insulin gene therapy" February 5, 2004

Indo-US Workshop on Tissue Engineering and Stem Cell Technologies, Sree Chitra Tirunal Institute for Medical Sciences, Trivandrum, India, "Hepatic insulin gene therapy in animal models of diabetes mellitus" February 4, 2004

"Hepatic Insulin Gene Therapy", Annual Fundraising Kick-Off, Atlanta Chapter, Juvenile Diabetes Research Foundation, April 22, 2003

The 1st International Symposium on Recent Progress in Gene & Cell Therapies for the Treatment of Diabetes Mellitus "Are we getting closer? Advances in Hepatic Insulin Gene Therapy", Yonsei University Medical Center, Seoul, Korea March 21, 2003

The 6th International Congress of the Cell Transplant Society, plenary session speaker, "Hepatocyte Targeted Insulin Gene Therapy", Atlanta, Georgia, March 2-5, 2003

"Are we getting closer? Advances in Hepatic Insulin Gene Therapy", Crawford W. Long Hospital, Department of Medicine Grand Rounds, February 14, 2003

"Hepatic Insulin Gene Therapy", Depts. of Physiology and Molecular Genetics, Research Conference, University of Tennessee, Memphis, October 30, 2002

"Metabolic and Secretory Organs" Session Co-Chair, Third Smith and Nephew International Symposium: Translating Tissue Engineering into Products, October 13-16, 2002

"Progress in Hepatic Insulin Gene Therapy", Avigen, Inc. Alameda, Calif. September 20, 2002

"Hepatic Insulin Gene Therapy", Beta-Society Annual Breakfast, New England Chapter, Juvenile Diabetes Research Foundation, June 9, 2002

"Advancing Hepatic Insulin Gene Therapy", Research Conference, Division of Endocrinology, Diabetes & Metabolism, University of Tennessee, Memphis, May 30, 2002

"Update: Oral Hypoglycemic Agents", Division of Geriatrics, Emory University School of Medicine, May 16, 2002

"Hepatic Insulin Gene Therapy", Annual Meeting, Tulsa, OK
Chapter, Juvenile Diabetes Research Foundation, March 6, 2002

"Progress in Hepatic Insulin Gene Therapy", Emory University Medical Grand Rounds, January 22, 2002

"Hepatic Insulin Gene Therapy", Annual Meeting, Houston, TX
Chapter, Juvenile Diabetes Research Foundation, Dec 2, 2001

"Hepatic Insulin Gene Therapy", Genzyme Corporation, Framingham, MA, June 22, 2001

"Hepatic Insulin Gene Therapy", Annual Meeting, Richmond, VA
Chapter, Juvenile Diabetes Research Foundation, June 16, 2001

"Advances in Insulin Gene Therapy", Crawford W. Long Hospital, Atlanta, GA, Medical Grand Rounds, March 30, 2001

" Gene Therapy into the Future", Columbus General Hospital, Medical Grand Rounds, Columbus Georgia, May 16, 2000

"Progress Toward Insulin Gene Therapy", Georgia Diabetes Research Consortium, Atlanta, GA, September 22, 1999

"A Model of Insulin Gene Therapy", Emory University, Medical Grand Rounds, April 14, 1998

23. **Bibliography:**

Peer Reviewed Publications:

1. Zinke H, Utz, D, Thulé PM, Taylor WF. Treatment options for patients with stage D_1 (T_{0-3}, N_{1-2}, M_0) adenocarcinoma of prostate. 1987, *Urology* 30(4):307-315

2. Robertson DG, Marino EM, Thulé PM, Seneviratne CK, Murphy LJ. Insulin and glucocorticoids regulate IGFBP-1 expression via a common promoter region. 1994, *Biochem Biophys Res Comm.* 200(1):226-232

3. Thulé PM, Thakore K, Vansant J, McGarity W, Weber C, Phillips LS. Preoperative localization of parathyroid tissue with technetium-99m sestamibi I^{123} subtraction scanning. 1994, *J Clin Endocrinol Metab.* 8(1):77-82

4. Huang S, Thulé PM, Phillips LS. Identification of novel promoter and repressor elements in the 5'-flanking regions of the rat IGFBP-1 gene. 1995, *Biochem Biophys Res Comm.* 206(1):279-286

5. Ziemer DC, Goldschmid MG, Musey VC, Domin WS, Thulé PM, Gallina, DL, Phillips LS. Diabetes in urban African-Americans. III. Metabolic control of Type II diabetes in a municipal hospital setting. 1996, *Am J Med.* 101(1):25-33

6. Krishna AY, Pao C-I, Thulé PM, Villafuerte BC, Phillips LS. Transcription initiation of the rat insulin-like growth factor-1 gene in hepatocyte primary culture. 1996, *Journal of Endocrinology.* 151(2):215-223

7. Thulé PM, Phillips, LS, Liu, J-M. Glucose Regulated Production of Human Insulin in Rat Hepatocytes, 2000, *Gene Therapy* 7(3):205-214

8. Thulé PM, Liu, J-M. Regulated Hepatic Insulin Gene Therapy of STZ-Diabetic Rats, 2000, *Gene Therapy,* 7(20):1744-1752

9. Olson DE, Paveglio SA, Huey PU, Porter MH, Thulé PM. Glucose Responsive Hepatic Insulin Gene Therapy of Spontaneously Diabetic BB/Wor Rats, 2003 *Human Gene Therapy*, 14:1401-1413

10. Porter MH, Paveglio SA, Zhang J-A, Olson DE, Campbell AG, Thulé PM. Host Cells Reduce Glucose Uptake and Glycogen Deposition in Response to Hepatic Insulin Gene Therapy, 2005, *Journal of Investigative Medicine* 53(4):201-212

11. Thulé PM, Campbell AG, Kleinhenz DJ, Olson DE, Boutwell JJ, Sutliff RL, Hart CM. Hepatic Insulin Gene Therapy Prevents Deterioration of Vascular Function and Improves Adipocytokine Profile in STZ-Diabetic Rats, 2006, *American Journal of Physiology-Endocrinology and Metabolism* 290:114-122

12. Cheng H, Nair G, Walker TA, Kim MK, Pardue MT, Thulé PM, Olson DE, Duong TQ. Structural and Functional Magnetic Resonance Imaging Reveals Multiple Retinal Layers, 2006, *Proceedings of National Academy of Sciences,* 103 (46) 17525-17530.

13. Hwang J, Kleinhenz D, Rupnow H, Thulé PM, Hart, CM. The PPARγ Ligand, Rosiglitazone, Reduces Vascular Oxidative Stress and NADPH Oxidase Expression in Diabetic Mice, 2007, *Vascular Pharmacology*, Jun; 46(6):456-62

14. Kozlowski M, Olson DE, Rubin J, Lyszkowicz D, Campbell A, Thulé PM. Adeno-associated viral delivery of a metabolically regulated insulin transgene to hepatocytes in

vitro and in vivo, 2007, *Molecular and Cellular Endocrinology,* Jul 15; 273(1-2):6-15

15. Mwangi S, Anitha M, Mallikarjuni C, Ding X, Hara M, Parsadanian A, Larsen CP, Thule P, Sitaraman SV, Anania F, Srinivasan S. Glial Cell Line-Derived Neurotrophic Factor increases beta cell mass and improves glucose tolerance, 2007, *Gastroenterology,* Mar; 134(3):727-737

16. Olson DE, Campbell AG, Porter MH, Freeman KG, Kelso E, Flatt WP, Thulé PM. Hepatic insulin gene therapy normalizes diurnal fluctuation of oxidative metabolism in diabetic BB/Wor rats, 2008, *Molecular Therapy*, 16: 1235-1242

17. Duong TQ, Pardue MP, Thulé PM, Olson DE, Cheng H, Nair G, Li Y, Kim M, Zhang X, Shen Q. *Invited review:* Layer-specific anatomical, physiological and functional MRI of the retina, 2008 *NMR in Biomedicine, Special Issue on MRI of Retinal and Optic Nerve Physiology,* 21(9):978-96

18. Olson DE and Thulé PM. *Invited review:* Gene Transfer to Induce Insulin Production for the Treatment of Diabetes Mellitus. 2008, *Expert Opinion on Drug Delivery,* 5(9):967-77

19. Li Y, Cheng H, Shen Q, Kim M, Thule PM, Olson DE, Pardue MT, Duong TQ, Blood-Flow Magnetic Resonance Imaging of Retinal Degeneration, *Investigative Ophthalmology and Visual Science,*2009, 50(4): 1824–1830

20. Bara H, Thulé PM, Sambanis A, Cell and Tissue-Based Therapies for Insulin-Dependent Diabetes, *Journal of Diabetes Science and Technology*, 2009 in press

21. Zhang J-A, Jia D, Olson DE, Campbell AG, Thulé PM Hepatic insulin gene therapy diminishes liver glycogen despite insulin responsive transcriptional effects in diabetic CD-1 mice, *Journal of Gene Medicine*, 2009, 11:588-597

Abstracts and Letters:

1. Gallina DL, Buchheit TE, Musey VC, Thulé PM, Ziemer DC, Odugbesan O, Goldstein S, Phillips LS. Evaluation of C-peptide/glucose ratio as a marker for treatment in Type II diabetes. AFCR, Southern Section, *Clinical Research* 39:838A, 1992.

2. Ziemer DC, Thulé PM, Musey VC, Brown SH, Phillips LS, Odugbesan O, Gallina DL. Prospective management of Type II diabetes in a municipal hospital setting. AFCR, Southern Section, *Clinical Research* 39:828A, 1992.

3. Thulé PM, Thakore K, Vansant J, McGarity W, Weber C, Phillips LS. Preoperative localization of parathyroid tissue with technetium-99m Sestamibi I^{123} subtraction scanning. ASCI, National Meeting, *Clinical Research* 41(2):153A, 1993.

4. Thulé PM, Seneviratne CK, Pao C-I, Marino EM, Noel CS, Murphy LJ, Robertson DG. Characterization of the rat IGFBP-1 promoter: Regulation by insulin. The Endocrine Society, 75th Annual Meeting, Abs. 1917, 1993.

5. Musey VC, Marshal KA, Thulé PM. Interim relief of glucotoxicity does not improve responses to oral agents in patients with NIDDM. Diabetes 44 (Suppl), American Diabetes Assoc., 55th Annual Meeting, 1995.

6. Thulé PM, Robertson DG, Marino EM, Huang S, Phillips LS. Impact of phorbol ester on transcription of the rat IGFBP-1 gene in rat hepatocyte primary culture. The Endocrine Society, 77th Annual Meeting, Abs. 296, 1995.

7. Thulé PM, Liu J. Regulated production of insulin from hepatocytes in primary culture. Diabetes 47 (Suppl 1), American Diabetes Assoc., 58th Annual Meeting, 1998.

8. Rich, JD, Dickinson, BP, Merriman, NA, Thulé PM. Insulin use by bodybuilders [letter]. JAMA 279(20):1613, 1998.

9. Thulé, PM, Liu J. Glucose-regulated human insulin production from hepatocytes in STZ-treated rats: a model of insulin gene therapy. Diabetes 48 (Suppl 1), American Diabetes Assoc., 59th Annual Meeting, 1999

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